REMARKS

Priority

The Examiner asserts that the application is not entitled to priority because the priority documents do not provide written description of the claimed invention and fail to establish utility or enablement. According to the Examiner, the priority date of the present application is its filing date of 8 May 2002.

Applicants reiterate that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to PCT Application PCT/US00/14042, filed 5/22/2000, which is a continuation-in-part and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/099812 filed 9/10/1998.

Applicants submit that for the reasons stated below, the claimed polynucleotides have a credible, substantial, and specific utility and were described in the priority documents. Applicants further maintain that the priority documents enable one skilled in the art to make and use the claimed invention.

Applicants note that the sequence of SEQ ID NO: 51 was first disclosed in US Provisional Application 60/099812 filed 9/10/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Accordingly, Applicants maintain that the present application is entitled to claim priority to US Provisional Application 60/099812 and PCT/US00/23328.

Utility

Claims 4-6, 11-14 and 16-31 were rejected on the assertion that the claimed subject matter lacks utility. The Examiner asserts that Applicants have provided a single analysis of

nucleic acid without any relative range for basing a utility of alleged over-expression in normal tissue and that no levels (relative or absolute) are particularly disclosed. According to the Examiner, the specification does not set forth the specifics with respect to a diagnostic assay such as the number of samples tested, the assay parameters, the probes/primer used and the normal and tumor ranges and statistical significance. The Examiner also asserts that the specification does not establish that the differences in mRNA levels were statistically significant. Hu et al is cited as cautioning against drawing any conclusions based on less than 10-fold differences in mRNA expression. The Examiner also asserts that the Declarations by Mr. Grimaldi, Dr. Polakis, and Dr. Ashkenazi were not persuasive.

Utility – Legal Standard

As previously noted, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

As previously noted, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its

scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the

evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polynucleotides have utility as diagnostic tools for cancer, particularly melanoma. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1411 polypeptide is expressed more highly in normal skin tissue compared to melanoma;

2. Applicants assert that, by virtue of their differential expression, the claimed polynucleotides have utility regardless of whether or not the encoded PRO1411 polypeptide is also differentially expressed. However, Applicnats maintain that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding **change** in the level of the encoded protein, e.g. an increase.

3. Applicants maintain that the specification provides sufficient information regarding the claimed differentially expressed polynucleotides to establish their utility, describe them, and enable on skilled in the art to use the claimed polynucleotides as diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO asserts that the specification fails to provide sufficient information regarding the statistical significance of the differential expression and how to use them as diagnostic tools.

2. The PTO cites Hu et al. to support its position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

As previously noted, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that Hu et al. is not contrary to Applicants' arguments, and therefore is not evidence to support the PTO's position. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Claims 4-6, 11-14 and 16-31 were rejected on the assertion that the claimed subject matter lacks utility. According to the Examiner, the relied upon utility (increased nucleic acid levels in normal tissue as compared to compared to melanoma) specifically requires or constitutes carrying out further research to identify or reasonably confirm a "real world"'context of use and as such is therefore not a "substantial utility." The Examiner maintains that the specification does not provide a specific and substantial or a well-established use. The Examiner asserts that Applicants have provided a single analysis of nucleic acid without any relative range for basing a utility of alleged over-expression in normal tissue and that no levels (relative or absolute) are particularly disclosed. According to the Examiner, the specification does not set forth the specifics with respect to a diagnostic assay such as the number of samples tested, the assay parameters, the probes/primer used and the normal and tumor ranges and statistical significance. The Examiner maintains that in order to be able to use a nucleic acid as a diagnostic, the skilled artisan must have the parameters in front of them.

Applicants maintain that the data in Example 18 demonstrates that the claimed polynucleotides are more highly expressed in normal skin compared to melanoma. In support of

this position, Applicants have previously submitted a copy of a first declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7).

As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added). The data presented in Example 18 show that the gene encoding PRO1411 is more highly expressed in normal skin tissue compared to melanoma. As the Grimaldi declaration indicates, the disclosed gene is therefore useful as a diagnostic tool.

Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be

used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

With respect to the Examiner's assertion that Applicants have provided a single analysis of nucleic acid without any relative range for basing a utility of alleged over-expression in normal tissue and that no levels (relative or absolute) are particularly disclosed, Applicants maintain that, as discussed above, the results of the analysis provide reliable data showing that the gene encoding PRO1411 is more highly expressed in normal skin tissue compared to melanoma. Furthermore, Applicants reiterate that the precise levels of gene expression are irrelevant. Rather it is the differential expression of the claimed polynucleotides which renders them useful as diagnostic tools.

According to the Examiner, the specification does not set forth the specifics with respect to a diagnostic assay such as the number of samples tested, the assay parameters, the probes/primer used and the normal and tumor ranges and statistical significance. The Examiner maintains that in order to be able to use a nucleic acid as a diagnostic, the skilled artisan must have the parameters in front of them.

Applicants maintain that one of skill in the art can readily utilize the claimed polynucleotides as diagnostic tools based on the differential expression described in the specification. The specification sets forth methods for measuring gene expression at Paragraph [0311]. Applicants further maintain that those of skill in the art are aware of many methods for quantitating nucleic acids which can readily be utilized in diagnostic assays involving the claimed polynucleotides. Similarly, one skilled in the art can readily design primers or probes capable of detecting the claimed polynucleotides in a sample. Likewise, those skilled in the art are readily able to apply known nucleic acid based diagnostic methodology to the claimed nucleic acids. Applicants maintain that the present situation is analogous to that in the caveat in Example 12 of the Revised Interim Utility Guidelines which states that the utility requirement is satisfied where the specification discloses that a protein is expressed in melanoma cells but not in normal skin because the disclosure of the receptor together with the knowledge of one skilled in the art supports the utility of the receptor and antibodies thereto as diagnostics.

Hu et al is cited as cautioning against drawing any conclusions based on less than 10-fold differences in mRNA expression. The Examiner asserts that the previously submitted Declarations in large part state conclusions based on experience and proffer no evidence with respect to the claimed nucleic acids. According to the Examiner, the specification as filed must supply the critical details for the correlation of a marker with disease and that the Declarations submitted by Applicants state conclusions based on experience and proffer no evidence with respect to the claimed nucleic acids. According to the Examiner, Hu et al and Haynes et al rebut the opinions expressed by the Declarants. The Examiner further maintains that one skilled in the cancer diagnostic art would not find it "more likely than not" that the mRNA levels are diagnostic of cancer in the absence of any report of specific levels, assay parameters and statistical variation thereof.

With respect to the Hu reference, Applicants reiterate that in Hu the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and

reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

Applicants note that there is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research with respect to therapeutics, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1411 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

With respect to the Haynes reference, Applicants note that Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a **change** in transcript level for a particular gene led to a **change** in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, (Gygi et al., Molecular and Cellular Biology, Mar. 1999, 1720-1730, previously submitted as Exhibit 5 with the Response to Office Action submitted March 16, 2005). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

Haynes reports that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold and that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to a increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

Furthermore, as discussed below, in view of their differential expression, the claimed polynucleotides possess utility regardless of whether or not the encoded polypeptides are also differentially expressed.

With respect to the Examiner's assertion that the specification as filed must supply the critical details for the correlation of a marker with disease, as discussed above, Applicants maintain that the data in Example 18 is reliable and that the disclosure of structure and the differential expression of the claimed polynucleotides is sufficient to allow one skilled in the art to use them as diagnostic tools.

With respect to the Examiner's assertion that the Declarations submitted by Applicants are insufficient, as discussed in more detail below, Applicants maintain that the Declarations are sufficient to establish the utility of the claimed polynucleotides. Applicants note that the Declarations are based on personal knowledge of the relevant facts at issue and are provided by experts in the relevant fields. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed above, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which the Declarations are based. Therefore, the PTO should accept the statements in the Declarations.

Furthermore, as noted above M.P.E.P. §2107 specifies that in most cases an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement. Where the Examiner rejects an application for lack of utility, the applicant may provide a Declaration under 37 C.F.R. §1.132 providing evidence of the asserted utility. (See M.P.E.P. §2107.02(VI)). Applicants maintain that the specification is sufficient to establish utility and that the submitted Declarations provide further evidence supporting Applicants' position.

The Examiner distinguishes *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d 1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) on the assertions that there is no claimed pharmaceutical composition, the issue is not correlation of in

vitro data with in vivo results, and the specification does not provide statistically significant results, relative ranges and the specific assay parameters for in vitro diagnostic assays.

Applicants maintain that, by virtue of their differential expression, the claimed polynucleotides are useful as diagnostic agents regardless of whether or not the encoded polypeptides are also differentially expressed. In addition, Applicants maintain that, in general, differential mRNA expression leads to differential expression of the encoded polypeptide. In this regard, Applicants assert that, just as the *in vitro* results in *Fujikawa v. Wattanasin* and *Cross v Iizuka* provided a reasonable probability that the claimed compounds would exhibit the asserted pharmacological behavior, the demonstration of differential expression of the PRO1411 polynucleotide provides a reasonable probability that the encoded polypeptide exhibits the asserted differential expression.

The Declaration of Dr. Grimaldi regarding pooled samples is asserted to be unpersuasive because it does not establish the particulars of individual variation and statistical significance of individual variation. The Examiner asserts that the specification does not define a normal range for the claimed nucleic acid or any variant thereof and that range is established using multiple samples.

Applicants maintain that, as stated in Paragraph 5 of the first Grimaldi Declaration, data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. In other words, if the variation were limited to a single member of the pool the effects of the variation would be minimized or masked by the lack of variation in the other members of the pool. Consequently, detection of variation in a pooled sample is more likely to reflect variation in each of the members or a majority of the members of the pool. Accordingly, Applicants maintain that, as provided in the Declarations of Mr. Grimaldi, the data in Example 18 is reliable. Furthermore, as discussed above, the precise levels of expression are irrelevant. In addition, as discussed above, Applicants maintain that one skilled in the art, armed with Applicants discovery that the claimed polynucleotides are differentially expressed, can readily utilize the techniques described in the specification or other techniques known in the art to use the claimed polynucleotides as diagnostic tools.

With respect to Mr. Grimaldi's statement that the results of Example 18 reflect at least a 2-fold difference in cDNA between tumor and normal counterpart, the Examiner asserts that the

details of the semi-quantitative analysis described by Declarant Grimaldi are not detailed in the specification as filed nor is the "at least 2 fold difference" of the declaration. According to the Examiner, the specification only teaches "more highly" and does not indicate that "more highly" is an at least a 2-fold difference.

As noted above, M.P.E.P. §2107 specifies that in most cases an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement. Where the Examiner rejects an application for lack of utility, the applicant may provide a Declaration under 37 C.F.R. §1.132 providing evidence of the asserted utility. (See M.P.E.P. §2107.02(VI)). Applicants maintain that the specification is sufficient to establish that the claimed polynucleotides are differentially expressed and the submitted Declaration provides further information regarding the experiments described in the specification.

The Examiner asserts that the differential expression of the mRNA is useful only if the differences are statistically significant from the normal as compared to the tumor/cancer and that the specification as originally filed does not establish this criticality for diagnostics.

As discussed above, Applicants maintain that the data in Example 18 are reliable and the specification provides sufficient information regarding the use of the claimed polynucleotides as diagnostics.

The Examiner asserts that the Declaration of Dr. Ashkenazi is not persuasive because more accurate tumor classification is not a contemplated utility of the specification and even if it was, there is no teaching of how to perform any of the asserted use for classification or determination of therapy for melanoma. According to the Examiner, the specification does not teach agents that target the gene product and does not permit a clinician to make any choice of tumor classification and therapy options.

Applicants maintain that the specification describes use of the claimed polynucleotides as well as their encoded polypeptides as diagnostic tools. Accordingly, one skilled in the art reading the specification would appreciate that one could use the claimed polynucleotides in conjunction with their encoded polypeptides as diagnostics as described in the Declaration by Dr. Ashkenazi. Applicants note that, consistent with Applicants' position, the Hanna reference describes the use of both nucleic acids and polypeptides as diagnostic tools for Her-2/neu.

With respect to the arguments based on the Hanna reference, the Examiner asserts that Hanna is not persuasive because in the present case the protein is overexpressed in normal, not in cancer cells and Hanna et al along with the art cited therein have clearly and unambiguously taught a role for Her-2/neu in certain breast cancers. According to the Examiner, the specification is devoid of such information with respect to the encoded protein and melanoma.

Applicants note that, by virtue of their differential expression, the claimed polynucleotides are useful as diagnostic tools regardless of whether or not the encoded polypeptides are also differentially expressed. Furthermore, Applicants maintain that the claimed polynucleotides are useful as diagnostic tools regardless of whether or not their differential expression is the causative agent of melanoma. As discussed above, the Hanna reference was provided simply to illustrate that, in some instances, it is beneficial to use both nucleic acid-based diagnostics and polypeptide-based diagnostics. Accordingly, Applicants maintain that Hanna supports Applicants' position.

A lack of known role for PRO1411 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes which are not the causative agent of cancer can nonetheless be used as diagnostic tools. In addition, the PTO's own written policies recognize that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state: "the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14); see also Exhibits 2-4 previously submitted with the Response to Office Action on March 16, 2005 (U.S. Patent Nos. 6,465,185, 6,228,582, and 6,162,604) (patents on polymorphisms which are indicative of a predisposition to a particular condition are patentable even though they may or may not cause the disease itself). Similarly, here the disclosed nucleic acids, as well as the encoded polypeptides and related antibodies, are useful for determining whether an individual has cancer regardless of whether or not they are the cause of the cancer.

The position of the PTO requiring a known role for PRO1411 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that there is at least a two-fold difference in PRO1411 cDNA between normal skin tissue and melanoma. Therefore, it follows that expression levels of the PRO1411 gene can be used to distinguish normal skin tissue from melanoma. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1411 polypeptide can also be used to distinguish normal skin tissue from melanoma. This provides additional utility for the claimed polynucleotides. In fact, the PTO has acknowledged the utility of similar nucleic acids based on the date in Example 18 in Applicants' related applications such as U.S. Patent Application Serial No. 10/063,676.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

As acknowledged by the Examiner (See Office Action at page 5), because the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression is not presently at issue. However, Applicants reiterate that they have established for the record that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO1411 polypeptide in melanoma, it is more likely than not that the PRO1411 polypeptide is also differentially expressed.

As discussed above, Applicants maintain that the claimed polynucleotides possess utility regardless of whether or not the encoded polypeptides are differentially expressed. However,

Applicants assert that it is more likely than not that a polypeptide encoded by a differentially expressed mRNA is differentially expressed. Applicants maintain that the Declarations of J. Christopher Grimaldi and Dr. Polakis, along with the previously submitted supporting references, confirm Applicants' position that it is more likely than not the polypeptides encoded by the claimed polynucleotides are also differentially expressed.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polynucleotides are differentially expressed in melanoma and that the claimed polynucleotides can be used as diagnostic and therapeutic tools. Given the lack of support for the PTO's position, Applicants

submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polynucleotides can be used as diagnostic agents for cancer, particularly melanoma.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polynucleotides

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1411 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polynucleotides.

As discussed above, there are significant data which show that the mRNA for the PRO1411 polypeptide is more highly expressed in normal skin tissue compared to melanoma. These data are strong evidence that the PRO1411 gene and polypeptide are associated with melanoma. Thus, Applicants submit that they have provided evidence associating the PRO1411 gene and polypeptide with a specific disease. The asserted utility of the claimed polynucleotides as a diagnostic tool for cancer, particularly melanoma, is a specific utility – it is not a general utility that would apply to the broad class of polynucleotides.

Conclusion

The PTO has asserted several arguments to support its conclusion that the differential expression of PRO1411 is not sufficient to establish utility for the claimed polynucleotides. The PTO asserts that the specification fails to provide sufficient information regarding the statistical significance of the differential expression and how to use them as diagnostic tools. The PTO also cites Hu et al. to support its position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants have previously provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. Applicants have pointed out that the substantial utilities described above are specific to the claimed polynucleotides because the PRO1411 gene

is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polynucleotides.

Second, Applicants have demonstrated that the specification provides sufficient information regarding the claimed polynucleotides to allow them to be used as diagnostic tools. Applicants have demonstrated that the precise levels of expression are not material but that, instead, the differential expression of the PRO1411 mRNA in melanoma compared to normal skin tissue provides utility for the claimed polynucleotides.

Third, Applicants maintain that the claimed polynucleotides are useful regardless of whether or not the encoded polypeptides are also differentially expressed. In addition, Applicants have shown that the previously submitted second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that polynucleotides encoding polypeptides which are differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polynucleotides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polynucleotides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Enablement

Claims 4-6, 11-14 and 16-31 were rejected on the assertion that, because the claimed subject matter lacks utility, one skilled in the art clearly would not know how to use the claimed invention.

As discussed above, Applicants maintain that the claimed polynucleotides possess utility. Accordingly, one skilled in the art would know how to use them.

Written Description

Claims 4-5, 12-14 and 16-31 were rejected on the assertion that they encompass subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

According to the Examiner, a single polynucleotide and a single polypeptide do not provide support for conception of variants. The Examiner asserts that specification fails to teach any variation of SEQ ID NO:51 or fragment thereof that is either from another species or which is a human variant isolated from nature. According to the Examiner, the sole single *human* polypeptide species described is PRO1411 of SEQ ID NO:51 and no written description is provided in the specification for any other species of PRO1411 molecules. The Examiner cites *Fiers v. Revel*, *Fiddes v. Baird*, *Univ. California v. Eli Lilly and Co.*, *In re Bell,* and *Fujikawa v Wattanasin* in support of her rejection. The Examiner also asserts that there is nothing in the hybridization claims that sets forth that the claimed nucleic acid is restricted to certain tumors as argued.

As previously noted, the subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:51, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:51, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203245, with the functional

recitation "wherein said isolated nucleic acid is more highly expressed in normal skin tissue compared to melanoma" or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO: 51" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO:51, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:51, the full-length coding sequence of the cDNA deposited under ATCC accession number 203245, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs."

Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO: 51, such that they hybridize to SEQ ID NO: 51 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to the decisions cited by the PTO. Unlike the situations in the cited decisions, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO: 51 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.

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> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

Given the degenerate nature of the genetic code, a large polypeptide is encoded by a vast number of different nucleic acid sequences. Yet the Court did not require the Applicants in *Wallach* to actually make and individually describe all of the sequences which encode the disclosed polypeptide sequence. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the polypeptide sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO: 51, and claim nucleic acids which are homologous to it and have the functional limitation of hybridizing to the disclosed sequence under the specified stringent conditions. It is routine in the art to create nucleic acids which have at least 95% or 99% sequence identity to SEQ ID NO: 51 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which nucleic acids will hybridize to the disclosed sequence under the specified conditions. This structure/function combination of a disclosed sequence and specified stringent condition is sufficient to describe the claimed nucleic acids. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus, or be able to visualize their detailed chemical structure, to adequately describe the genus.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:51 with the functional recitation "wherein said isolated nucleic acid is more highly expressed in normal skin tissue compared to melanoma" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also

have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in melanoma. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

In view of the foregoing, Applicants submit that the subject matter encompassed by Claims 4-5, 12-14 and 16-31 is adequately described in the specification.

Statement Regarding Biological Deposit

Claims 4-6, 13, 14 and 26-31 were rejected as failing to comply with the enablement requirement. The declaration pursuant to 37 CFR 1.808 was asserted to be insufficient to obviate this rejection because it was not signed by an attorney of record over his/her registration number.

While Applicants disagree with the grounds of this rejection and believe the previously provided Declaration is sufficient, Applicants submit another Declaration herewith providing the registration number of the signatory.

Prior Art

Claims 4-6, 14 and 16-31 were rejected under 35 U.S.C. 102(e) on the assertion that they are anticipated by Baker et al (WO 01/64888).

Applicants reiterate that the present application claims priority to U.S. Provisional Patent Application Serial No. 60/099812, filed Sept 10, 1998 while the earliest priority date of the cited PCT application is March 1, 2000. In addition, Applicants note that both the present application and WO 01/68848A2 claim priority to PCT/US00/14042 and PCT/US00/23328. Accordingly, Applicants maintain that in view of the foregoing, the cited PCT application is not prior art under 35 U.S.C. §102(e), since it was not filed before Applicants invention of the claimed subject matter.

Claims 4-6, 11-14 and 16-31 were rejected under 35 U.S.C. 102(e) on the assertion that they are anticipated by Baker et al. (U.S. PreGrant Publication US2003/0027275, U.S. Patent Application Serial No. 10/176918). Applicants reiterate that the present application claims priority to U.S. Provisional Patent Application Serial No. 60/099812, filed Sept 10, 1998 while the earliest priority date of the cited U.S. application is Sept. 16, 1998. Applicants further note that both US2003/0027275 and the present application claim priority to PCT/US99/20111, PCT/US00/14042, and PCT/US00/23328. In view of the foregoing, Applicants maintain that US2003/0027275 is not prior art under 35 U.S.C. §102(e) since it was not filed before Applicants invention of the claimed subject matter.

Claims 4-6, 11-14 and 16-31 were rejected under 35 U.S.C. 102(b) on the assertion that they are anticipated by Ashkenazi et al (WO 00/77037, published December 12, 2000).

As discussed above, Applicants maintain that the present application is entitled to priority date of 9/10/1998 and the data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. As the December 21, 2000 publication date of Ashkenazi is not more than one year before either 9/10/98 or 8/24/2000, Applicants maintain that Ashkenazi (WO 00/77037) is not prior art under 35 U.S.C. §102(b).

New Rejections

Claims 14, 16 and 21-25 were rejected under 35 U.S.C. 112, second paragraph, on the assertion that they are indefinite. The Examiner asserts that the terminology "at least about X nudeotides in length" is indefinite because the recitation of "at least" indicates that the isolated nucleic acid should have the minimum number of nucleotides but that, in combination with the term "about" which provides for a range above and below the indicated "X nucleotides in length" the lower limit is unclear and ambiguous.

Applicants note that the specification at Paragraph [0012] defines the terminology "about" as the referenced nucleotide sequence length plus or minus 10% of that referenced length. Accordingly, Applicants maintain that the terminology "at least about X nucleotides in length" is definite.

Claims 14 and 21-25 were rejected under 35 U.S.C. 102(b) on the assertion that they are anticipated by Valenzuela et al. (WO 99/55721, published November 4, 1999). Valenzuela et al is asserted to teach a nucleic acid that has at least 300 consecutive nucleotides in common with SEQ ID NO:51 (see attached alignment with AAZ43802). According to the Examiner, the sequence described in Valenzuela et al. inherently hybridizes under stringent conditions absent convincing evidence to the contrary.

As discussed above, Applicants maintain that the present application is entitled to priority date of 9/10/1998 and the data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. As the November 4, 1999 publication date of Valenzuela is not more than one year before either 9/10/98 or 8/24/2000, Applicants maintain that Valenzuela et al. (WO 99/55721) is not prior art under 35 U.S.C. §102(b).

Conclusion

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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